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Influence of Some Factors on Cadmium Pharmacokinetics and Toxicity

by Krista Kostial,* D. Kello,* Maja Blanuša,* Tea Maljković,* and I. Rabar*

Cadmium metabolism in the young and in conditions of dietary contamination with ash from coal gasification were investigated.

The experiments were performed in adult rats which received ash in the diet (5%) and/or cadmium in drinking water (100 ppm) over a period of five weeks and in sucklings whose mothers were given the same treatment throughout pregnancy and lactation. In pharmacokinetic studies, ^{115m}Cd was administered orally or intraperitoneally to determine the intestinal absorption, retention, and distribution. Cadmium toxicity (LD_{50}) was determined in different age groups of animals treated with ash for five weeks before a single oral or intraperitoneal administration of cadmium chloride.

After intraperitoneal administration, ^{115m}Cd body retention decreased with age and was independent of the dietary treatment. Sucklings had a higher retention in the blood, carcass, and gut than adults. After oral administration, sucklings had a much higher body retention than adults regardless of the dietary treatment of their mothers. Cadmium toxicity was also independent of the dietary treatment. Most striking was a very high oral toxicity of cadmium in sucklings.

It is concluded that the young might be at a special risk at the same level of environmental cadmium exposure because of the high oral cadmium toxicity at this age which is most probably due to a high cadmium retention in the gut. It is also concluded that the mixture of elements contained in ash is not likely to influence cadmium metabolism and toxicity in conditions of dietary exposure.

Introduction

Although cadmium is one of the best investigated toxic metals other than lead, data on factors which might interact with cadmium metabolism and cause changes in cadmium toxicity are still insufficiently known and relatively poorly understood. Most of the available data on cadmium interaction have been obtained with other metals and in extreme experimental conditions. Recently it was recognized that factors other than metals could be of importance for metal toxicology and alter the dose-effect and dose-response relationship (*1*). Among these factors, age at the time of exposure might be one of the most important (*2*).

The purpose of this work was to provide new evidence on two major topics: on cadmium metabolism and toxicity in the young as a potentially more sensitive population group and on cadmium metabolism in conditions of dietary contamination with ash (slag) from coal processing, because of a possible interaction of elements in ash with cadmium health effect. Our experiments were performed on rats of different ages fed a diet containing ash additive from a coal gasification plant. We studied pharmacokinetics and toxicity of cadmium in adult rats and in their offspring. We determined cadmium pharmacokinetics by using radioactive cadmium and toxicity by administering cadmium chloride orally or intraperitoneally. Our previous results on the effect of age and other dietary treatments on cadmium metabolism (*2–5*) are also included for comparison. Our results indicate that the young might be at a higher risk than adults since they show a much higher oral cadmium toxicity, most probably because of a higher cadmium absorption and higher cadmium retention in the gut. Diet with ash additive had almost no influence on cadmium metabolism and toxicity either in adult rats or in their offspring.

* Institute for Medical Research and Occupational Health, Moše Pijade 158, 41000 Zagreb, Yugoslavia.

Methods

Animals

All experiments were performed on random bred albino rats from our own animal house. Animals were of both sexes aged between 1 and 52 weeks. Suckling rats were kept in litters (reduced to six one day after birth) and placed in individual cages with their mothers. Weanling rats (aged three weeks) and older animals were housed in plastic cages in groups of 10–15 animals per cage.

Dietary Treatment

Ash Additive to Diet and Cadmium Additive to Drinking Water. Ash (slag) from a coal gasification plant (REMHK Kosovo, Obilić) was dried to a 4% moisture content and ground to particles not exceeding 50 μm in diameter. Chemical and spectrochemical analysis of some ash components was performed at the Mining Institute in Zemun, and detailed data will be presented elsewhere (*6*). The experimental diet was prepared by addition of 5% (w/w) of ash to the powdered control diet which was then pelleted in the Pliva pharmaceutical works, Zagreb (producers of our rat diet), in the same way as the control diet. The content of various elements in both diets is presented in Table 1.

Cadmium in concentration of 100 ppm (0.1 g Cd/l.) was added to deionized water as chloride and supplied to animals from drinking bottles with stainless steel sipper tubes.

Adult rats received ash in the diet and/or cadmium in drinking water over a period of five weeks. The same treatment was used for female rats throughout the pregnancy and lactation period in experiments with sucklings.

Other Dietary Treatments. Milk-fed animals received cow's milk one week before pharmacokinetic studies (*4*). In animals fed low (0.3%) and high (2.4%) calcium diets, pharmacokinetic studies were performed after 32 weeks of pretreatment (*5*). Details of the pharmacokinetic studies have been given elsewhere (*4*, *5*).

Table 1. Some elements in control diet and diet with ash additive.[a]

Element	In control diet, mg/g	With ash (5%) in diet, mg/g
Ca	12.00	25.96
Zn	0.06	0.06
Fe	0.60	2.46
Cu	0.05	0.05
Mn	0.16	0.22

[a] Analyzed by AAS method.

Pharmacokinetic Studies

In pharmacokinetic studies ^{115m}Cd (specific activity 0.5–1.0 mCi/mg Cd, purchased from the Radiochemical Centre, Amersham, England) was administered orally or intraperitoneally. In sucklings the artificial feeding method (*7*) was used for oral administration. The oral dose contained about 15 μCi ^{115m}Cd in 0.5 ml of cow's milk. In other age groups of animals, the oral dose contained between 40 and 60 μCi ^{115m}Cd, and it was administered by stomach tube. The intraperitoneal dose contained 10–20 μCi ^{115m}Cd.

The retention of radioactive cadmium was determined 6–7 days after administration in sodium iodide scintillation counters (Tobor double crystal assembly, Nuclear Chicago, was used for whole body and carcass determinations and an automatic gamma counter, Nuclear Chicago, for organ distribution studies). During this period rats received the same diet as during the pretreatment period.

After intraperitoneal administration the radioactivity was determined in the whole body, blood, liver, kidneys, and carcass (whole body after removal of the intestine, liver, kidneys, and blood). Blood values were corrected to theoretical blood content in animals of matching weight and age according to Belcher and Harriss (*8*). Gut retention was also calculated by subtracting the retention in the liver, kidneys, blood, and carcass from the whole body retention.

After oral administration the radioactivity of cadmium was determined in the whole body with and without the intestinal tract and from these values gut retention was also calculated. The results are expressed as percentage of the administered dose and presented as arithmetic means and standard error of the mean.

Toxicity

The toxicity of cadmium was determined in animals of different ages treated with ash for five weeks before a single oral or intraperitoneal administration. Cadmium chloride ($CdCl_2 \cdot H_2O$) was given by stomach tube in a volume of 0.5 ml/100 g of body weight. Six dose levels were used in each age group. Each dose level was tested in six animals. The LD_{50} values and the 95% confidence limits were calculated by the method of moving averages (*9*) 8 days after a single oral or intraperitoneal administration.

Table 2. Whole body retention of cadmium in relation to age and diet after intraperitoneal administration.[a]

Age, weeks	Cd, % dose ^{115m}Cd[b]				
	Control diet	Milk diet	Ash (5%) in diet	Cd 100 ppm in water + control diet	Ash (5%) in diet + Cd 100 ppm in water
1	96.73 ± 0.72 (22)[c] 92.78 ± 1.71 (12)		91.42 ± 2.92 (12)	93.41 ± 1.43 (12)	95.32 ± 0.97 (12)
2	95.77 ± 0.63 (9)[d]				
3	87.30 ± 1.60 (10)[c]				
6	82.06 ± 0.90 (9)[c] 82.35 ± 0.78 (9)[c]	82.26 ± 0.94 (10)[c]			
18	82.61 ± 0.69 (12)		81.19 ± 0.66 (12)	80.85 ± 0.95 (12)	83.60 ± 0.89 (12)
52	72.36 ± 0.62 (10)[c]				

[a] All results were obtained 7 days after radioisotope administration except values from Kello and Kostial (*3*), which were obtained 6 days after administration. All animals were females except sucklings which were of both sexes.
[b] Values are presented as arithmetic means ± SE. Number of animals in parentheses.
[c] Data from Kello and Kostial (*3*).
[d] Data from Kello and Kostial (*16*).
[e] Data from Kello and Kostial (*4*).

Table 3. Distribution of cadmium in relation to age and diet.

Diet	Animal age	Cd, % dose ^{115m}Cd 7 days after intraperitoneal administration[a]				
		Liver	Kidneys	Blood	Carcass[b]	Gut[c]
Control diet	Sucklings, 1 wk	44.66 ± 0.91	2.23 ± 0.12	0.48 ± 0.04	30.08 ± 2.16	15.23 ± 1.62
Ash (5%) in diet	Sucklings, 1 wk	47.66 ± 0.38	1.98 ± 0.06	0.48 ± 0.04	29.25 ± 0.81	14.55 ± 1.24
Cd (100 ppm) + control diet	Sucklings, 1 wk	45.95 ± 1.25	2.25 ± 0.27	0.36 ± 0.04	30.30 ± 1.63	14.54 ± 1.43
Ash (5%) in diet + Cd (100 ppm)	Sucklings, 1 wk	48.74 ± 0.71	2.00 ± 0.05	0.33 ± 0.04	28.11 ± 0.67	16.60 ± 0.76
Control diet	Adults, 18 wk	65.56 ± 0.80	3.37 ± 0.08	0.24 ± 0.01	10.75 ± 0.54	2.76 ± 0.83
Ash (5%) in diet	Adults, 18 wk	64.59 ± 0.80	3.50 ± 0.07	0.23 ± 0.01	10.54 ± 0.34	1.50 ± 0.83
Cd (100 ppm) + control diet	Adults, 18 wk	63.16 ± 1.16	3.89 ± 0.08	0.25 ± 0.02	9.88 ± 0.25	3.40 ± 0.89
Ash (5%) in diet + Cd (100 ppm)	Adults, 18 wk	66.33 ± 0.76	3.69 ± 0.07	0.27 ± 0.01	10.53 ± 0.34	2.77 ± 0.62

[a] Values of 12 animals in each experimental group are presented as arithmetic means ± SE.
[b] Percentage radioactivity in the body determined after removal of the intestinal tract, liver, kidneys, and blood.
[c] Calculated values obtained by subtracting percentage retention in liver, kidneys, blood, and carcass from the percentage whole body retention values from Table 2.

Results

Influence of Age and Dietary Treatment on Cadmium Pharmacokinetics

Cadmium Retention and Distribution. The whole body retention determined 6 or 7 days after a single intraperitoneal administration of ^{115m}Cd was high and practically independent of the dietary treatment (ash additive or milk diet) or stable cadmium concentration in drinking water. The retention decreased with age from about 95% in sucklings to 72% in 52 week-old rats, i.e., it decreased by a factor of about 1.3 (Table 2).

The distribution of cadmium in the liver, kidneys, blood, and carcass was independent of the ash content in the diet and/or cadmium concentration in drinking water (Table 3). The age effect on cadmium distribution was, however, very obvious. Suckling rats retained a lower percentage of cadmium in the liver (about 1.4 times) and kidneys (about 1.7 times) and higher in the blood (about 1.6 times) and carcass (about 2.8 times). The calculated gut values in suckling rats were about six times those in adult rats, indicating the intestine as the site of selective cadmium accumulation in the young.

Cadmium Absorption from the Intestine. The highest absorption values were observed in suckling rats, ranging from about 21 to 39% (Table 4). In litters from mothers which were treated with stable cadmium additive the values were slightly lower

Table 4. Retention of cadmium in relation to age and diet after oral administration.[a]

Age, weeks	Sample[b]	Cd, % dose ^{115m}Cd						
		Control diet	Milk diet	Ash (5%) in diet	Cd (100 ppm) in water + control diet	Ash (5%) in diet + Cd (100 ppm) in water	Low Ca diet (0.3%)	High Ca diet (2.4%)
1	W.B.	26.61 (24)[c] 2.02						
	W.B.	38.46 (12) 3.38		36.31 (12) 1.82	20.96 (12) 2.58	23.81 (12) 0.71		
	W.B.-I.	7.51 (12) 0.77		6.47 (12) 0.41	6.59 (12) 0.26	7.75 (12) 0.18		
3	W.B.	0.89 (10)[c] 0.03	15.78 (11) 0.62					
6	W.B.	0.49 (10)[c] 0.02	6.86 (10) 0.24					
18	W.B.	0.59 (12) 0.04		0.81 (12) 0.15	0.45 (12) 0.05	0.80 (12) 0.13		
	W.B.-I.	0.47 (12) 0.03		0.67 (12) 0.11	0.38 (12) 0.04	0.71 (12) 0.14		
52	W.B.	0.32 (10)[c] 0.06	5.60 (8)[c] 0.39					
	W.B.	0.45 (9)[d] 0.05					0.61 (8)[d] 0.06	0.12 (8)[d] 0.01

[a] All data were obtained 7 days after p.o. administration except data from Kello and Kostial (*4*) and Kello et al. (*5*), which were determined 6 days after oral administration. All animals were females except sucklings, which were of both sexes. Values are presented as arithmetic means ± SE. Number of animals in parentheses.

[b] W.B. = whole body; W.B.-I. = whole body without intestine.

[c] Data from Kello and Kostial (*4*).

[d] Data from Kello et al. (*5*).

than in other groups.

A sudden decrease of cadmium absorption occurred after weaning when values in all experimental groups decreased to less than 1%. Only animals fed the milk diet showed much higher absorption values in all age groups. In animals between the age of 3 and 52 weeks a trend towards a decreased absorption with increasing age was observed. The lowest values were observed in the oldest age group, especially in rats fed the high calcium (2.4%) diet. The ash-treated 18-week-old group of female rats had slightly higher values than the controls.

The variations in results in sucklings are due to the fact that although there were at least 12 animals in each group they were only from two litters. Animals from several litters should be used for evaluating possible statistical differences between various groups of sucklings. A similar difficulty occurs when differences in absorption between various groups of adult rats are evaluated because of the very low percentage absorption at this age. Much larger groups of animals should be used for estimating the statistical significance of small differences in absorption due to dietary treatment.

After removal of the intestinal tract, values in all groups of sucklings were greatly reduced, indicating that most (about 75%) of the high cadmium whole body retention was located in the gut. In adult rats (18 weeks old) the removal of the intestinal tract caused only a small decrease (about 15%) in the whole body retention indicating a much lower cadmium retention in the gut in older age groups of animals.

Influence of Age and Dietary Treatment on Cadmium Toxicity

Intraperitoneal Toxicity. The acute intraperitoneal cadmium toxicity was age- but not sex-related (Table 5). The results were independent of the dietary treatment. Lowest LD_{50} values, indicating highest toxicity, were observed in the oldest group of rats. Suckling rats showed LD_{50} values which were similar to values obtained in other age groups (3–18 weeks).

Oral Toxicity. The acute oral cadmium toxicity was also age-related (Table 6). Highest toxicity was observed in the youngest group of rats, and it was not influenced by ash additive to the mother's diet. After weaning a sudden decrease in cadmium tox-

Table 5. Toxicity of cadmium in relation to age and sex 8 days after a single intraperitoneal administration of $CdCl_2$.[a]

Age, weeks	LD_{50} values (95% confidence limits), mg/kg	
	Males	Females
2[b]	10.7 (10.0-11.4)	
	7.6 (6.8- 8.5)	
3	14.5 (12.2-17.3)	11.8 (9.4-14.8)
6	7.6 (5.2-11.2)	8.5 (6.9-10.5)
18	11.0 (6.9-17.6)	9.6 (7.0-13.1)
52	2.0 (1.7- 2.4)	1.8 (1.4-2.2)

[a] Six dose levels of $CdCl_2$ were used in each age and sex group (six rats were used for each dose level tested). $CdCl_2$ was given in a volume of 0.5 ml/100 g of body weight.
[b] Sucklings were of both sexes.

icity was observed. The animals which received ash additive had slightly lower LD_{50} values in some experimental groups. In the oldest group of rats an increase in oral cadmium toxicity was noticed. The oral toxicity values were practically the same in male and female rats. Our previous finding of a lower oral absorption of cadmium in males (*5*) might not be relevant for interpreting the results of toxicity studies in which very high doses of cadmium are used for LD_{50} determination.

Discussion

The influence of age on the metabolism of several metals has been observed by many authors (*10*). Cadmium metabolism in sucklings has many similarities with the metabolism of some other metals at this age (i.e., lead, mercury, manganese) which is characterized by a higher whole body retention, specific organ distribution, higher intestinal absorption, and higher oral toxicity (*2*). However, our present results also show some specific features in cadmium metabolism in sucklings which have not been observed with other metals. The age-related decrease in cadmium whole body retention after intraperitoneal administration is not specific for cadmium since a similar decrease with age has also been observed in lead (*11*), mercury (*12*), and manganese (*2*) retention in rats. The lower percentage of cadmium in the kidneys of sucklings is in agreement with results reported by Gunn and Gould (*13*), who found significantly lower kidney values at an early interval (24 hr) after radioactive cadmium administration in the young. In our earlier study (*3*), we found, with the same experimental procedure, higher cadmium retention in the kidneys of sucklings at a later interval after intraperitoneal administration (2 weeks). This indicates that redistribution of cadmium in the body of sucklings still occurs within this period. The ability of cadmium to mobilize from other tissues and to accumulate in the kidneys is well known (*14*). Kotsonis and Klaassen (*15*) assume that the redistribution of cadmium to the kidneys in time is due to the longer time period required to increase the metallothionein levels in the kidney.

The finding that young animals have a higher retention of cadmium in the "rest" of the body than in critical organs (kidneys and liver) has been already commented on in our earlier paper (*3*). Part of the high carcass retention in sucklings is obviously caused by a higher hair and skin retention. We found for cadmium but not for lead that the content in the hair is age-dependent and due to a higher selective cadmium accumulation in the hair of young animals and therefore concluded that hair might not be a good indicator of the total body burden of cadmium (*16*). The finding that a part of the higher whole body cadmium retention in sucklings

Table 6. Toxicity of cadmium in relation to age, sex and diet 8 days after a single oral administration of $CdCl_2$.[a]

Age, weeks	LD_{50} values (95% confidence limits), mg/kg			
	Control diet		Ash (5%) in diet	
	Males	Females	Males	Females
2[b]	47.0 (43.0-51.0)[c]			
	18.4 (15.5-22.0)			
	12.7 (10.5-15.3)		12.7 (10.5-15.3)	
3	227 (162-317)	240 (198-291)[c]		
6	260 (207-328)	211 (182-252)[c]		
18	202 (136-299)	170 (140-206)[c]		
	166 (144-197)	168 (137-207)	135 (107-172)	145 (116-180)
52	145 (116-180)	109 (86-136)[c]		
	131 (106-162)	128 (106-154)	92 (71-115)	95

[a] Six dose levels of $CdCl_2$ were used in each age, sex and dietary group (six rats were used for each dose level tested). $CdCl_2$ was given by stomach tube in a volume of 0.5 ml/100 g of body weight.
[b] Sucklings were of both sexes.
[c] Data from Kostial et al. (*2*).

is due to the higher retention in the gut, even after intraperitoneal cadmium administration, is also interesting. In conditions of oral exposure most of the higher whole body retention in sucklings is due to a higher cadmium accumulation in the gut. A similar finding was made by Sasser and Jarboe (*17*), who found a longer residence time of cadmium in the intestinal tract and a greater absorption of cadmium in the newborn. They assumed that the prolonged retention of ^{115m}Cd by the intestinal tract is the result of adsorption of cadmium on the intestinal mucosa and uptake of cadmium by the epithelial crypt and lymphatic cells. In similar experimental conditions, the high whole body retention observed in sucklings after oral application of radioactive lead was however almost entirely due to lead absorption without an increased lead retention in the gut (*18*), while the high body retention observed for cerium in young animals (*19*) was found to be due to a hold-up by intestinal mucosa cells.

The sudden decrease in cadmium absorption after weaning (at the age of 3 weeks) is in agreement with other experimental data (*17, 20*) and it was previously observed for several other metals (*2, 10*).

Our intraperitoneal LD_{50} data do not indicate that sucklings are an age group especially susceptible to cadmium toxicity. We reached a similar conclusion in lead toxicity studies in rats (*21*). We tried to explain the greater resistance of the young to heavy metal lethal action by a lower level of "free metal" in the immature organism (*22*). Only oldest animals of both sexes showed an increase in the acute intraperitoneal cadmium toxicity. In this age group pharmacokinetic results indicate lowest cadmium whole body retention.

In conditions of oral exposure, cadmium is very toxic to sucklings. This is indicated by the small differences between the oral and intraperitoneal LD_{50} values in this age group. The ratio between these two values is only about 3 in sucklings; it increases in animals aged from 3 to 18 weeks to values between 16 and 34, reaching values of about 70 in the oldest animals. Comparative data on oral and intraperitoneal mercury and manganese toxicity obtained in this laboratory show a similar trend with age. However, the ratio between the oral and intraperitoneal LD_{50} values in sucklings was about 15 for mercury and about 8 for manganese; i.e., it was never as low as for cadmium (unpublished data).

A high gut retention accompanied by a very high oral toxicity is therefore specific for cadmium metabolism in sucklings. Sucklings also absorb a much higher fraction of cadmium in conditions of oral exposure. This absorbed fraction, although retained in the rest of the body in the early distribution phase, is likely to be redistributed in the body and to cause a higher cadmium concentration in the kidneys at a later stage.

Of all dietary treatments only milk diet caused great changes in cadmium absorption. Milk was previously found to increase intestinal absorption of other metals (lead, mercury, manganese), and the possible mechanism of this action has been commented on elsewhere (*2, 4, 23*). For this effect of milk it seems essential that milk only is present in the intestine, which might indicate that metal absorption is greatly dependent on the intestinal contents. Since then, we found that not only milk, but also several other diets increase lead absorption in rats (*24*). We concluded that the bioavailability of lead and other metals might be greatly dependent on dietary habits and much higher in rats on "human" diets than in animals on standard rat food. More data on the bioavailability of toxic metals in rats on "human" diets would be useful, since these results are more similar to absorption values obtained in humans, and also since the very low percentage absorption of toxic metals in animals on standard rat chow makes the evaluation of small differences in intestinal absorption due to dietary treatments very difficult.

The increase in the stable cadmium intake did not affect any of the pharmacokinetic parameters in adult rats. Only in suckling rats did the percentage gut retention after oral administration seem to be lower, possibly because of some saturation mechanism in the process of intestinal gut retention at this age. However, this is disputable, since amounts of cadmium which are transferred from mother to fetus and litter during pregnancy and lactation are supposed to be relatively low (*14*) and since more data are required before such a statement is made.

Addition of ash to the diet had almost no effect on cadmium pharmacokinetics and toxicity. It is astonishing how little information is available on the synergistic or antagonistic effects of a mixture of elements as contained in ash, although available information suggests potential problems and need for such research (*25*). The ability of a mixture of metals to interact, i.e., to produce synergistic or antagonistic health effects is dependent on many variables. It is difficult to evaluate whether metals contained in our ash sample from the coal gasification plant were biologically available. The diet with ash additive had about two times higher calcium content and about four times higher iron content, i.e., a higher content of some elements which are known to be relevant for cadmium absorption (*1*). A similar increase in the calcium content of the diet caused decreased cadmium absorption in our previous experiments (*5*). This could be due to the influ-

ence of other elements in ash besides calcium on cadmium absorption. The mechanism of the metal–metal interaction is generally poorly understood. Many interactions have been demonstrated only with high doses of toxic metals and often in condition of parenteral administration. Also, many more data on the influence of metals on cadmium absorption were obtained in conditions of trace elements deficiency than in conditions of metal additives as in our experiments.

A pretreatment with low doses of metals was previously found to cause protection against acute lethal effects of metals probably because of the induction of metal binding protein synthesis (*1*). In our experiments pretreatment with ash caused almost no changes in acute cadmium toxicity. This could be due to the interaction between elements contained in the ash which might otherwise induce such a protein synthesis.

Conclusion

More information is needed to evaluate the potential risk at oral cadmium exposure, especially in the young. In sucklings, because of the high intestinal absorption, high gut retention, and high oral toxicity, the intestine could be almost considered the "critical organ" for cadmium. More data on the mechanism of intestinal cadmium absorption are obviously needed. The bioavailability of cadmium should be studied in conditions in which human dietary cadmium contamination is likely to occur, i.e., from a complex mixture of elements occurring together at low levels in food and water. The bioavailability of cadmium will depend not only on interaction with these elements in the process of absorption, distribution, and retention, but also on other dietary conditions, especially age at the time of exposure. Such a complex experimental approach might be the only way to obtain results applicable for future environmental exposure conditions.

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